

CLINICAL EVALUATION OF FLEROXACIN IN THE TREATMENT OF BONE AND JOINT INFECTIONS

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Abstract. The objective of this open label, non-comparative study was to evaluate the efficacy and safety of fleroxacin 400mg administered orally once daily to patients with acute osteomyelitis and/or acute septic arthritis. Nineteen patients (10 males and 9 females) were evaluable for the analysis of clinical efficacy and safety. Of these, 7 (36.8%) had osteomyelitis and 12 (63.2%) had septic arthritis. Bacteriological cures were reported in 6 of 7 patients (85.7%) with osteomyelitis and in 8 of 11 patients (72.7%) with septic arthritis. The median duration of treatment for the clinical cures in osteomyelitis and septic arthritis were 29.5 days and 46 days respectively. The eradication rate for the most common pathogens, *Salmonella enteritidis* and *Staphylococcus aureus* were 77.7% and 80.0%, respectively. The clinical response was cure in 4 of 7 patients (57.1%) evaluable for osteomyelitis, and in 9 of 12 patients (75.0%) evaluable for septic arthritis at the three-month follow-up after treatment. Adverse reactions were minimal. It is concluded that fleroxacin appears to be an effective and safe in the treatment of acute osteomyelitis and acute septic arthritis.

INTRODUCTION

Fleroxacin (RO 23-6240/AM 833) is a novel antimicrobial agent, belonging to the class of fluorinated 4-quinolones (Wolfson and Hooper, 1989). Fleroxacin combines an extremely broad antimicrobial spectrum (Chin *et al*, 1986) with a long elimination half-life (T_{1/2} 10-12 hours) (Weidekamm *et al*, 1988) and excellent penetration into biologic fluids and tissues (Nakashima *et al*, 1988). *In vitro* susceptibility tests show that the predominant pathogens of bone and joint infections, such as *Staphylococcus aureus* in normal healthy adult and *Salmonella* species in systemic lupus erythematosus (Cohen *et al*, 1987), are highly susceptible to fleroxacin (Chin *et al*, 1986; Manek *et al*, 1986). The objective of this study was to evaluate the efficacy and safety of fleroxacin in adult patients with acute osteomyelitis and acute septic arthritis with or without bacteremia.

MATERIALS AND METHODS

This is a prospective, open label, non-comparative trial with patients receiving fleroxacin

400 mg once daily for 2 to 12 weeks, with visits after 5 to 9 days of therapy, subsequently every 2 weeks during therapy, 0 to 3 days after the end of therapy, 4 to 6 weeks and 3 months after treatment end. The study population was recruited from hospitalized patients treated at Taipei and Kaohsiung Veterans General Hospitals. The diagnosis of acute osteomyelitis and acute septic arthritis, with or without bacteremia, were based on the presence of pathogenic organisms at the site of infection and the following clinical signs and symptoms: for osteomyelitis, radiologic or biopsy evidence of osteomyelitis and temperature > 38°C orally, pain, erythema, swelling or heat of overlying soft tissue and drainage from sinus tract or surface ulceration; for septic arthritis, temperature > 38°C orally, pain on motion or limitation of motion and increased synovial fluid in joint.

A medical history was taken, demographic data recorded, details of any concomitant medication recorded, a physical examination (including temperature and vital signs) was performed, a check for clinical symptoms and signs was made.

Appropriate specimens were obtained and cultured before starting treatment, and at the visits during treatment and at follow-up. Samples for osteomyelitis were taken by bone biopsy, by aspiration of purulent material from below the skin surface, or from purulent bony material obtained during surgery; Those for septic arthritis were obtained by aspiration of synovial fluid. Blood samples were cultured initially at baseline. Cultures were repeated at the later assessment time points if the baseline culture was positive. Susceptibility to fleroxacin was determined by *in vitro* disk diffusion using modified NCCLS methods (NCCLS, 1984).

It must be pointed out that in several instances repeat cultures were not physically possible (deep bone and joint infections) where access to site of infection was no longer feasible or a superficial sinus had closed.

In some instances for these same reasons, whilst clinical failure from prior therapy evident, there was no possibility for collection of a fresh isolate in the transition period between previous failed treatment and starting fleroxacin. This problem is intrinsic to this type of clinical study, so that the clinical outcome is more relevant in these circumstances than bacteriological follow up. The exceptions to this are the few treatment failures with fleroxacin where repeat isolates were obtainable.

The outcome of treatment with fleroxacin was judged on the basis of both bacteriological and clinical responses. The bacteriological outcome at end of treatment was determined as follows: cure, all initially pathogenic organisms eradicated at the time of follow-up culture, or the lesion is healed and no material is available for culture; failure, a failure is regarded as proven by a single positive culture showing persistence of an original causative pathogen during the treatment to the last day of the follow-up. The clinical outcome was assessed as follows: clinical cure, presenting clinical symptoms disappeared and laboratory findings (ESR) associated with the primary diagnosis normalized at the time drug was discontinued and during follow-up; clinical improvement, presenting clinical symptoms and laboratory findings (ESR) subsiding significantly but with incomplete resolution of clinical evidence of infection at

end of treatment; clinical failure, no apparent clinical response to treatment.

Possible toxicity was assessed on each patient treated with fleroxacin, including a daily interview and examination, a complete blood count and differential count, a platelet count, urinalysis, and tests of liver and renal function performed before, during and after treatment.

RESULTS

A total of 19 patients was evaluated including 7 patients (36.8%) with acute osteomyelitis and 12 patients (63.2%) with acute septic arthritis. Table 1 summarizes the demographic data of the populations included in the safety analysis and in the analysis of efficacy. The major symptoms of osteomyelitis and septic arthritis were swelling, pain, erythema, and limited movement (data not shown). Of the 7 patients evaluable for osteomyelitis, the infection was located in the lower extremities (foot, tibia and femur) of 3 patients, in the sternum of 2 patients, in the spine of 1 patient and in the finger of 1 patient. Of the 12 patients evaluable for septic arthritis, the infection was located in the lower extremities (mainly the knee) of 10 patients, and in the upper extremities of 2 patients. The number of patients with concomitant diseases from the start of the study up to the time follow-up are given in Table 1.

Bacteriological outcome

In 18 of 19 patients, causative organisms were identified. The one with culture-negative septic arthritis considered to be gonococcal arthritis because gram stain of synovial fluid showed gram-negative cocci intra-cellular paired. Table 2 presents the summary of the bacteriological outcome by pathogen for 18 culture-positive patients. Overall, the majority of pathogens isolated were eradicated. The eradication rate for the most commonly isolated pathogens, *Salmonella enteritidis* was 7 of 9 patients (77.7%) and for the *S. aureus*, was 4 of 5 (80.0%). All other pathogens were eradicated except one strain of beta-hemolytic *Streptococcus*. All persisting pathogens (2 *S. enteritidis* and 1 *S. aureus*) remained susceptible to fleroxacin except 1 strain of beta-hemolytic *Streptococcus*. Table 3 presents a summary of the bacteriological outcome by infection for all patients.

Table 1
Demographic data summary.

Parameter	n = 19
Sex	
Males	10
Females	9
Age at treatment (years)	
Mean	52.89
Median	60
Range	21 - 74
Concomitant diseases	
Systemic lupus erythematosus	5
Diabetes mellitus	2
Gouty arthritis	1
Myasthenia gravis	1
Carcinoma of cervix	1

Table 2
Summary of bacteriological outcome by pathogen.

Organisms	No. eradicated/No. isolated (%)
<i>Salmonella enteritidis</i>	7/9 (77.7)
<i>Staphylococcus aureus</i>	4/5 (80.0)
beta-hemolytic <i>Streptococcus</i>	1/2 (50.0)
<i>S. epidermidis</i>	1/1
<i>Pseudomonas aeruginosa</i>	1/1
Total	14/18 (77.7)

For osteomyelitis, 6 of 7 patients (85.7%) were bacteriologically cured, and 1 of 7 (14.3%) was failure. The persisting pathogen at follow-up was susceptible *S. enteritidis*. The median duration of treatment for patients bacteriologically cured of infection was 29.5 days (range : 28-49 days). Those who failed had received treatments for 42 days. For septic arthritis, 8 of 11 patients (72.7%) were bacteriologically cured, and 3 of 11 (27.3%)

Table 3
Summary of bacteriological outcome by infection.

Infections	n = 18
Osteomyelitis	
No. of patients	7
Cure	6 (85.7%)
Failure	1
Septic arthritis	
No. of patients	11
Cure	8 (72.7%)
Failure	3

were failures. The three pathogens which persisted were *S. enteritidis* 1, *S. aureus* 1, and beta-hemolytic *Streptococcus* 1. The median duration of treatment for patients bacteriologically cured of infection was 46 days (range : 14-64 days). The three with bacteriological failures had received treatment for 4, 7 and 56 days respectively.

Clinical outcome

Table 4 summarize the assessment of the clinical outcome for all patients. For osteomyelitis, of the 7 evaluable patients, 4 (57.1%) were clinically cured, 3 (42.9%) were improved, there were no failures. The 3 patients with clinical improvement included the one who had a bacteriological failure yet susceptible *S. enteritidis* infection, and the other two patients had concomitant bacteremia. For septic arthritis, of the 12 evaluable patients, 9 (75.0%) were clinically cured, 1 (8.3%) was improved, and 2 (16.7%) were failures. The one clinically improved patient was bacteriologically cured and the organism was a moderately susceptible *Pseudomonas aeruginosa*. The 2 clinical failures were also bacteriological failures and both had bacteremia. Table 5 shows the bacteriological outcome for the patients who were not clinically cured. The majority of those who were not clinically cured were also bacteriological failures.

Safety results

All 19 patients treated with fleroxacin were monitored for adverse events and abnormal re-

Table 4

Summary of assessment of clinical outcome.

Infections	n = 19
Osteomyelitis	
No. of patients	7
Cure	4 (57.1%)
Improvement	3 (42.9%)
Failure	0
Septic arthritis	
No. of patients	12
Cure	9 (75.0%)
Improvement	1 (8.3%)
Failure	2 (16.7%)

Table 5

Summary of bacteriological outcome for the patients not clinically cured.

Clinical outcome	Bacteriological outcome					
	Osteomyelitis			Septic arthritis		
	n	cure	failure	n	cure	failure
Improvement	3	2	1	1	1	0
Failure	0	0	0	2	0	2

sults of laboratory tests (Table 6). Eight of 19 patients complained of adverse events, the most frequent being nausea and vomiting, with spontaneous recovery in all patients. The most frequently encountered abnormal laboratory tests were decreased hematocrit, elevated serum aspartate aminotransferase (SGOT) and serum alanine amino transferase (SGPT), but the level reverted to normal soon after discontinuation of fleroxacin administration. No treatment was interrupted due to fleroxacin administration. As treatment coincided with active, it is difficult to ascertain relationship of adverse events to treatment, disease or both.

DISCUSSION

Since the introduction of nalidixic acid in 1963, many quinolone derivatives have been synthesized and marketed. The first generation compounds (nalidixic acid, cinoxacin, oxolinic acid) were confined to the treatment of urinary tract infections because of their narrow antibacterial spectrum limited to a few *Enterobacteriaceae* and their pharmacodynamic profile (Ronald *et al*, 1966). The second generation of quinolones (pivemidic acid, flumequine, acrosoxacin) appeared in about 1970 and was distinguished from the first by a wider spectrum of activity and significant, although variable, activity against *P. aeruginosa*, and generally, by a more powerful effect on some *Enterobacteriaceae* than the previous compounds. The second generation compounds still remained limited to treatment of urinary tract infections for same reasons as did the first generation quinolones. The third generation of quinolones (norfloxacin, pefloxacin, ciprofloxacin, ofloxacin, enoxacin, fleroxacin) was first introduced "chemically" with flumequine, the first fluorinated quinolone, and is characterized by a very wide spectrum of antibacterial activity including *Staphylococcus* and all the *Enterobacteriaceae*, even those that are not very sensitive to the third generation cephalosporins, and by powerful activity against sensitive organisms (Hooper and Wolfson, 1991). Fleroxacin produces a serum peak of between 5µg/ml (single dose) and 10µg/ml (steady-state) after either parenteral or oral administration of 400 mg (Brain *et al*, 1986, Weidekamm *et al*, 1988).

Table 6

Number of patients with clinical adverse events and laboratory abnormalities (N = 19).

Adverse reactions	Number
Nausea	4
Vomiting	3
Epigastric pain	1
Hyperventilation syndrome	1
Insomnia	1
Decreased hematocrit	3
Decreased hemoglobin	1
Elevated SGOT/SGPT	3

Gram-positive cocci, especially *S. aureus*, are the predominant causative organisms in patients with bone and joint infections. On the other hand, *Salmonella* species is the most frequent causative pathogen in such infections in hemoglobinopathies and systemic lupus erythematosus (Cohen *et al*, 1987). *In vitro* susceptibility tests show that *S. aureus* and *Salmonella* species are highly susceptible to the third generation quinolones (Chin *et al*, 1986). However, they have only borderline activity against other bacteria such as *Enterococcus*, *Streptococcus*, *P. aeruginosa* and other *Pseudomonas* species, (Chin *et al*, 1986; Hooper and Wolfson, 1991; Brain *et al*, 1986).

Clinical information regarding the treatment of osteomyelitis or arthritis is not yet available for a larger series of clinical trial in quinolones except for ciprofloxacin. (Gentry and Rodriguez, 1990; Greenberg *et al*, 1987; Hoogkamp-Korstanje *et al*, 1989; Norden and Shinnors 1985; Peterson *et al*, 1989). Only a few patients with *Salmonella* osteomyelitis and arthritis treated with third generation quinolones has been reported (Brain *et al*, 1986).

Satisfactory results in the treatment of acute osteomyelitis and acute septic arthritis of fleroxacin are evident in this clinical trial. Nineteen patients (10 males and 9 females) were evaluable for the analysis of efficacy. Their mean age was 52.89 (range : 21-74) years. Of these, 7 (36.8%) had osteomyelitis and 12 (63.2%) had septic arthritis. Bacteriological cures were reported in 6 of 7 patients (85.7%) with osteomyelitis and in 8 of 11 patients (72.7%) with septic arthritis. The eradication rate for the most common pathogen, *S. enteritidis* was 7 of 9 (77.7%), and for *S. aureus* was 4 of 7 patients (57.1%) evaluable for osteomyelitis. Of the remaining 3 patients (42.9%) were clinically improved and no patients were assessed as clinical failures. Clinical cures were reported in 9 of 12 patients (75.0%) evaluable for septic arthritis. Of the remaining patients, 1 (8.3%) was clinically improved and 2 (16.7%) were failures. Both clinical failures were also bacteriological failures (Table 5)

Adverse reactions, mainly nausea and vomiting occurred. Abnormal laboratory tests, mainly decreased hematocrit and elevated SGOT/SGPT occurred. However, there was no need to discontinue the drug due to clinical adverse reactions or abnormal laboratory tests.

In conclusion, the results of this study indicate that fleroxacin administered in an oral single daily dose schedule is effective and safe in the treatment of acute osteomyelitis and acute septic arthritis, but a larger number of patients is necessary to confirm this results.

In addition, as referred to above, bacteriological proof of failed previous treatment prior to onset of fleroxacin, is highly desirable to provide unequivocal proof of treatment effect. Since cure however is usually clinical (no specimen collection feasible except for occasional joint effusion), intrinsic to this study is the difficulty of fresh isolate collection compared with the usual clinical bacteriological infections.

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